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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/809,127	MCCULLERS, JONATHAN A.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/06/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-20 and 34-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific secondary bacterial infection (e.g., pneumonia, bacterial sinusitis, otitis media) with the administration of oseltamivir phosphate, zanamivir and peramivir), does not reasonably provide enablement for "preventing secondary bacterial pneumonia", "attenuating a secondary infection...the bacterial infection is prevented...", "attenuating a secondary infection...to prevent..." or "a neuraminidase inhibitor ". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is

the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method for preventing a secondary infection in a subject infected with an influenza virus, namely a secondary bacterial pneumonia in patients afflicted with viral influenza, comprising administering a neuraminidase inhibitor.

Websters II Dictionary defines the term "prevent" as "anticipate or counter in advance, to keep from happening". The interpretation of the instant claims allows for the complete cure and eradication or total elimination of said secondary infection by the administration of said agent.

The specification defines that "neuraminidase inhibitor" refers to "analogues of sialic acid".

With respect to the scope of enablement for "preventing" said secondary infection,

There are no known compounds of similar structure which have been demonstrated to prevent pneumonia or secondary infection as complication of influenza viral infection. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "magic bullet" is contrary to our present understanding of pharmacology.

Contrary to the instantly claimed invention, it is known today that pneumonia caused by virus, particularly influenza virus, is very difficult to treat. At this time, there is

not proven medicantion to treat or prevent pneumonia caused by the influenza virus ("Pneumonia", Healthwise, Hehnert, Paul., 2005). Thus, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" or completely cure or eradication effect.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant compounds.

The specification provides the effects of oseltamivir phsophate in reducing secondary bacterial pneumonia, lobar bronchopneumonia infection due to influenza virus (Examples, particularly Example 5). However, there is no demonstrated correlation that the tests and results apply to the claimed preventive utility embraced by the instant claims.

Since the efficacy of the claimed compound(s) in preventing the secondary bacterial infection, particularly pneumonia, otitis media, sinusitis due to influenza virus mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for "a neuraminidase inhibitor" or "a secondary bacterial infection",

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of treating or preventing secondary bacterial infection or pneumonia as sequelae to a viral influenza prior to filling of the instant invention was an unpredictable art.

The claims are very broad due to the vast number of possible compounds of that are described as being "a neuraminidase inhibitor" or multiple complex disorders having unrelated manifestations due to influenza infection.

The instant claims cover not only the treatment or prevention of upper respiratory tract infection such as pneumonia, sinusitis, ear infection and pharyngitis, but also lower tract infection such as UTI (urinary tract infection) or skin infection such as MRSA infection (methicillin-resistant ***Staphylococcus aureus*).** Furthermore the scope of "a neuraminidase inhibitor" includes that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

As discussed above, although the specification provides the effects of oseltamivir phsophate in reducing secondary bacterial pneumonia, lobar bronchopneumonia infection due to influenza virus (Examples, particularly Example 5), there is no demonstrated correlation that the tests and results apply to the claimed therapeutic utility of treating all secondary infections embraced by the instant claims, for example UTI or MRSA infection associated with influenza virus.

In addition, although the specification discloses oseltamivir phosphate, zanamivir, peramavir, as the suitable "a neuraminidase inhibitor", the specification fails to provide how to make/screen "a neuraminidase inhibitor" without undue amount of experimentation. As discussed in preceding comments, in the instant case, only a limited number of examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The instant claims read on any compounds having "a neuraminidase inhibitor", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575.

As discussed above, considering above factors, especially the "sufficient working examples", "the level of skill in the art", "the relative skill and the unpredictability in the pharmaceutical art", "breadth of the claims" and "the chemical nature of the invention", one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the claimed methods of prevention or treatment.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-8, 12, 15 and 18-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 6, the phrase "including" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, the claim 6 recites the broad recitation "chronic metabolic diseases" and "immunosuppression", and the claim also recites "including diabetes mellitus" and "including immunosuppression caused by medications or by human immunodeficiency [HIV] virus" respectively which is the narrower statement of the range/limitation.

Regarding claims 2, 8, 21-22 and 26-27, the claims contain the trademark/trade name "RJW-270201 (BCX-1812)", "Unasyn", "Timentin" and "Augmentin" respectively. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe peramivir, ticarcillin/clavulinic acid, ampicillin/sulbactam, amoxicillin/clavulinic acid, respectively and, accordingly, the identification/description is indefinite.

Regarding claims 12 and 15, the claims recite "mycoplasma species". It is not clear what "mycoplasma species" refer to. Does it refer to mycoplasma pneumoniae? Or refer to other species related to mycoplasma?

Regarding claims 1-8, 18-27, the phrases "an effective amount" renders the claim indefinite because the claim includes elements not actually disclosed which could mean the administering of the compound is for any therapy, thereby rendering the scope of the claim unascertainable. See MPEP 2173.05(d). The "preventing secondary bacterial pneumonia", "treating pneumonia" and "treating a secondary bacterial infection" in the

preamble of claims 1, 18 and 23 respectively may be implied as being what is meant for "an effective amount" but this is implied at best. An implied limitation is not clear and concise as required under 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 14-15 and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Hayden, F.G. (Vaccine, Vol. 19, 2001, S66-S70).

Hayden teaches that anti-influenza neuraminidase inhibitors such as zanamivir and oseltamivir is beneficial in reducing otitis media as a sequelae to viral influenza infection.

Claims 4-11, 13-14 and 16-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Kaiser et al. (Arch Intern Med. Vol. 160, 2000, pp. 3234-3240).

Kaiser teaches that the administration of the claimed neuraminidase inhibitor such as zanamivir (twice or four times a day for 5 days) to a patient (at least 12 years old including subjects 65 years or older or those with a chronic illness, including cardiopulmonary conditions and diabetes) afflicted with laboratory confirmed influenza infection (defined by the presence of fever or feverishness with at least 2 additional symptoms such as cough, sore throat, headache or myalgia) less than 2 days' duration decreases the respiratory complications or worsening of symptoms (i.e., pneumonia,

acute sinusitis, otitis media, acute bronchitis) leading to antibiotic use (abstract; 'Patients and Methods' in page 3235; Tables 3-5); and the treatment of patient receiving antibiotic prescription (i.e., penicillins, macrolides, cephalosporins, sulfonamides and quinolones) for a respiratory tract complication (i.e., acute bronchitis, acute sinusitis, pharyngitis, ear infection including otitis media, pneumonia) or worsening of initial symptoms as a complication or sequelae to a viral influenza infection, which occurred within approximately 6 days after the onset of symptoms, with the zanamivir reduces said respiratory tract events (Figure 1A and 1B; 'Outcomes and Effect of Treatment' in page 3236; 'Antibiotics' in page 3237; 'Discussion').

Although Kaiser is silent about "prevent a pathogenic synergism between the virus and a bacterial agent that characteristically promotes a severe bacterial infection wherein the bacterial infection is prevented from disseminating throughout the subject's lung tissue" (claim 9), "wherein the pathogenic synergism results from the effects of influenza-virus mediated cleavage of terminal sialic acid from epithelial cells lining the subjects' lungs" (claim 10), "the pathogenic synergism results from viral neuraminidase-mediated exposure of pneumococcal receptors on lung epithelia cells" (claim 11), "prevention of pathogenic synergism restricts a lower respiratory tract infection to a focal process that is characteristic of primary pneumococcal pneumonia as opposed to a severe bacterial infection that disseminates throughout the subject's lung tissue" (claim 13), or "prevent a pathogenic synergism between the virus and a bacterial agent that characteristically mediates a secondary bacterial infection of the respiratory tract" (claim 14), such characteristics or properties must be inherent to the claimed neuraminidase inhibitor such as zanamivir. The prior art directing the administration of same compound,

in overlapping dosage amounts (see page 19, lines 27-29 of the specification), to same patient group (i.e., pneumonia, sinusitis, ear infection or otitis media) inherently possessing therapeutic effect for the same ultimate use as disclosed by the instant invention anticipates the instant invention even absent explicit recitation of underlying mechanism.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-3, 12, 15 and 18-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaiser et al. (Arch Intern Med. Vol. 160, 2000, pp. 3234-3240), and further in view of Applicant's admitted prior art of record (page 9, line 26 thru 10, line 25) and The Merck Manual ("Pneumonia", Fifteenth Edition, 1987, pp. 657-665).

The teaching of Kaiser has been discussed in above 35 USC 102(a) rejection. In addition, Kaiser discloses oseltamivir (oral) as functional equivalent to zanmivir that is useful in reducing respiratory complications of patients afflicted with community-acquired influenza in which is leading to antibiotic prescription (page 3239, column 1, lines 32-39).

Applicant's admission and the Merck Manual are being as a supplemental references to demonstrate that influenza infections are known to increase the susceptibility of an infected to particular bacterial infections caused by species of bacterial pathogens such as pneumococcus, staphylococcus, myocplasma, non-group H. influenza and moraxella catarrhalis; S. pneumoniae is the most common cause of bacterial pneumonia and accounts for approximately two-thirds of bacteremic community-acquired pneumonias; and a presumptive diagnosis of pneumonia can be based on combination of physical examination and patient history, changes in chest X-ray, more specifically the detection of lobar consolidation, the detection of a bacterial pathogen by Gram-stain examination of sputum, a positive quelling reaction, and/or culture of a bacterial organism from sputum samples.

The teaching of Kaiser differs from the claimed invention in (i) the bacterial infection medicated by an organism selected from the group consisting of: Streptococcus pneumoniae, Staphylococcus, aureus, Haemophilus influenzae, mycoplasma species and moraxella catarrhalis" and (ii) the step of diagnosing patient afflicted with the influenza and bacterial pneumonia as "difficulty breathing accompanied by a chest examination that indicates rales; consolidation on chest X-ray; and at least one indicator selected from the group consisting of fever, high white blood cell count and a productive cough"; and

(iii) the administration of said neuraminidase inhibitor (i.e., zanamivir) to a subject "who has been symptomatic for viral influenza for more than 48 hours".

One having ordinary skill in the art would have been known as evidenced by Applicant's admission and the Merck Manual that the secondary infection, particularly pneumonia often caused by s. pneumoniae, is effectively treated by zanamivir or in combination with zanmivir and antibiotics. Furthermore, one having ordinary skill in the art

With respect to the specific time requirement, generally differences in an time periods will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such time periods are critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable time periods by routine experimentation.

Although the instant claims use the different names for the said ingredients than those taught in the cited references, these references are particularly pertinent and relevant because all the claimed species and their roles are well taught in the cited reference. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

5. No Claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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